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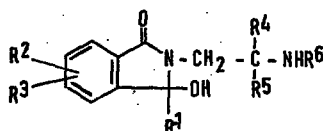


(54) NOVEL PHTHALIMIDINE COMPOUNDS

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 10017, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to certain sulphonated phthalimidines useful as intermediates.

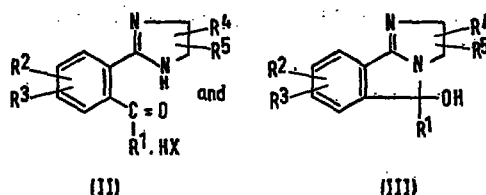
The invention provides new compounds having the following general formula



(I)

where R¹ is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R² is hydrogen, halogen, amino, (lower)alkylamino, (lower)alkyl or (lower)alkoxy; R³ is hydrogen when R² and R³ are dissimilar and when R² and R³ are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; R⁴ and R⁵ are hydrogen or (lower)alkyl, R⁶ is (lower)alkylsulphonyl, phenylsulphonyl, monohalophenylsulphonyl, dihalophenylsulphonyl, mono(lower)alkylphenylsulphonyl, di(lower)alkylphenylsulphonyl or (lower)alkoxyphenylsulphonyl.

These compounds are useful intermediates for preparing compounds possessing pharmacological activity. In particular compounds of the invention are useful in the preparation of new compounds of the general formulae



(II)

(III)

where R¹, R² and R³ are as defined above; R⁴ and R⁵ are both (lower)alkyl and are attached to the same carbon atom; and X is the anion portion of a pharmacologically acceptable acid addition salt. These compounds are described and claimed in our U.K. Application 46940/70 (Serial No. 1 325 065). This invention also concerns processes which may be applicable in the production of compounds disclosed in U.K. Specification No. 1,229,652. The novel compounds of formulae II and III exhibit antidepressant activity but unlike the compounds of U.K. Specification No. 1 229 652 they do not possess anorectic activity at therapeutic doses.

In the above formula I R⁴ and R⁵ both preferably represent methyl in the new compounds possessing utility as intermediates for preparation of new compounds according to Application 46940/70 (Serial No. 1 325 065). Where the new compounds of the invention possess utility as intermediates for the production of compounds disclosed in U.K. Specification No. 1 229 652 R⁴ and R⁵ represent hydrogen. Illustrative examples of R¹ include phenyl; *m*-chlorophenyl; *p*-chlorophenyl; *p*-fluorophenyl; *p*-iodophenyl; *p*-bromophenyl; *o*-chlorophenyl; 3,4-diodophenyl; 3,4-dichlorophenyl; 2,5-dibromophenyl; *m*- and *p*-trifluoromethylphenyl; *p*-tolyl; 3,4-dimethylphenyl; *p*-methoxyphenyl; 3,4-dimethoxyphenyl; 2-thienyl; 2-pyridyl and 2-furyl. R² and R³ preferably represent hydrogen. Where R² is a substituent it preferably represents fluorine, bromine, chlorine, iodine, methoxy, ethoxy, methyl or ethyl. Illustrative examples of R⁶ include *p*-tolylsulphonyl; ethylsulphonyl; *n*-pentylsulphonyl; phenylsulphonyl; *p*-fluorophenylsulphonyl; *p*-chlorophenylsulphonyl; *p*-bromophenylsulphonyl; *p*-iodophenylsulphonyl; 2,5-dichlorophenylsulphonyl; 3,4-dibromophenylsulphonyl; 3,4-difluorophenylsulphonyl; 4-ethylphenylsulphonyl; 3,4-dimethylphenylsulphonyl; 3,4-diethylphenylsulphonyl; *p*-methoxyphenylsulphonyl and *p*-ethoxyphenylsulphonyl.

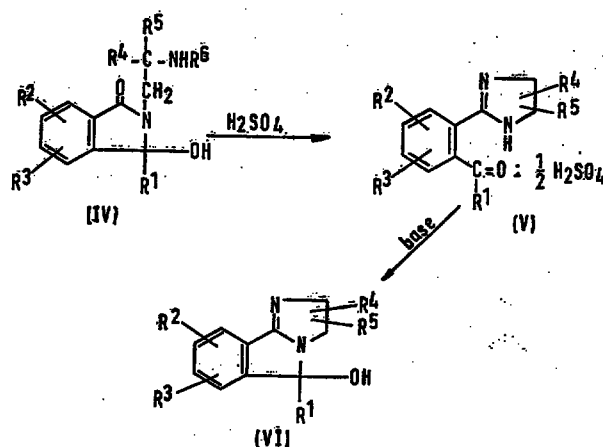
As employed herein the term "(lower)alkyl" is meant to include straight and branched chain hydrocarbon moieties of from 1 to 5 carbon atoms such as methyl, ethyl, propyl, *i*-propyl and butyl. The term (lower)alkoxy is used to include saturated hydrocarbonyloxy groups which contain from 1 to 6 carbon atoms such as methoxy, ethoxy, propoxy, butoxy and hexoxy. The terms "halogen" and "halo" as used herein are meant to include bromine, fluorine, chlorine and iodine.

Those skilled in the art will appreciate that the compounds of formulae II and III are tautomers. It has been found that the base form (III) exists as the tricyclic imidazoisindole form and the acid-addition salt (II) exists as the aromatic ketone form. The nature of the reaction by which the compounds are prepared does not allow the position of the gem-dialkyl groups to be fixed with certainty. When the compound exists as the aromatic ketone form, it is impossible to fix the position of the gem-dialkyl

groups because of the proton shift due to the —NH—C=N— group. Hence, the 2-(gem-dialkyl-2-imidazolin-2-yl)benzophenone acid addition salts are named as 4,4-(5,5)dialkyl-substituted compounds. This is in conformity with the nomenclature for imidazole compounds set forth in Heterocyclic compounds R.C. Elderfield, Editor, Vol. 5, pp 198, 199 and 238, John Wiley and Sons, Inc., New York, 1957. When the imidazoisindol-ol form of aromatic ketone tautomer is formed, the tautomerism of the

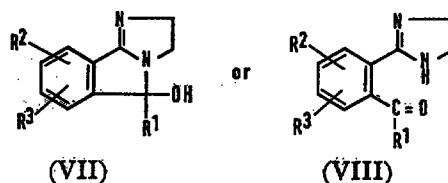
HN—C=N— moiety does not permit any absolute prediction as to positioning of the gem-dialkyl group in the imidazoisindol-ol form. When the steric influence of the gem-dialkyl group is considered, the probability is great that the product obtained is a 2,2-dialkyl compound. Gas chromatographic studies indicate a single compound is isolated and not a mixture of the 2,2-dialkyl and 3,3-dialkyl isomers. As the available evidence does not conclusively eliminate the possibility of the formation of the 3,3-dialkyl compound, the alternative nomenclature is employed herein, although it is believed that the structure is in actuality a 2,2-dialkyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol.

The compounds of formulae II and III may be prepared by contacting the appropriate phthalimidine with a strong acid such as sulphuric acid and subsequently treating the product with a base:



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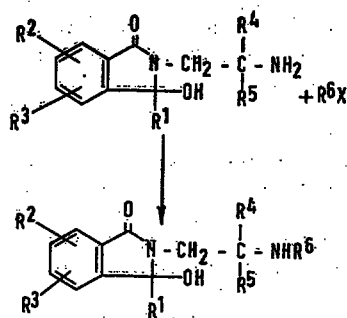
wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same as herein above defined for formulae II and III and R^6 is the same as defined above for formula I. In addition, this method is operable for the production of compounds wherein R^4 and R^5 are hydrogen. Thus the present invention particularly provides a process of preparation of a compound of formula



where desired in the form of an acid addition salt, wherein a compound of formula I where R^4 and R^5 are both hydrogen is treated with a strong acid, and, if desired an acid addition salt form of the product is converted into the free base form of a free base form into an acid addition salt form.

Concentrated sulphuric acid of 75 or 80—100% strength is preferably employed as the strong acid. Generally, no criticality attaches to the use of a particular basic compound when the sulphate salt is treated to prepare the imidazoisoindol-ol base form. For example, sodium carbonate, sodium hydroxide, potassium hydroxide or sodium bicarbonate may be used. When the tautomeric acid-addition salt is to be prepared, the preferred method is to saturate a lower alkanolic solution of the base form of the compound with hydrogen chloride gas. Suitable lower alkanols include methanol, ethanol and propanol.

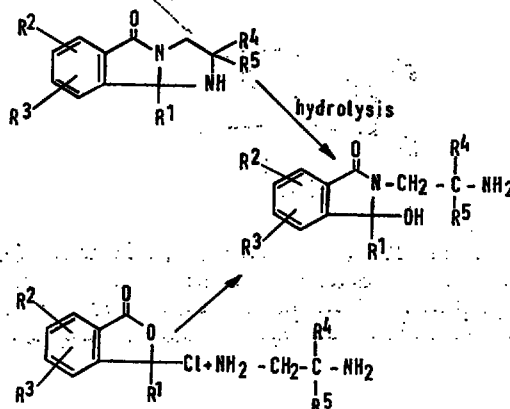
The intermediate sulphonated phthalimidines may be prepared as follows:



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as above defined and X is a halogen atom. The sulphonation is usually conducted in pyridine, e.g. at 25°C to 115°C for 4 to 8 hours, although other suitable organic or aqueous solvents, with a base such as sodium carbonate or triethylamine, may be employed. The reactants can be refluxed for about

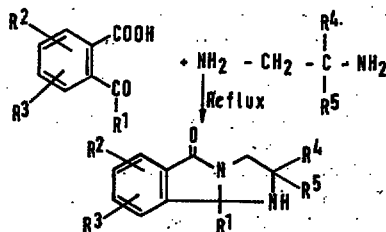
12 to 24 hours, the solvent is evaporated and the residue is partitioned between water and an immiscible organic solvent such as ethyl acetate, ether, chloroform or benzene. The organic portion is separated and then the solvent is evaporated. The residue is recrystallised from a lower alkanol such as methanol, ethanol or propanol to yield the sulphonated product.

The phthalimidines may be obtained by the hydrolysis of an imidazoisindolone or by reaction of the ϕ -acid chloride of an *o*-aroyl-benzoic acid with the appropriate ethylenediamine:



wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are the same as hereinabove defined. The reaction with the ethylenediamine is carried out in a solvent under reflux until the reaction is complete.

The imidazoisindolone compounds may be prepared by condensing an ethylenediamine with the appropriate aroyl-benzoic acid:



wherein R^1 , R^2 , R^3 , R^4 and R^5 are the same as hereinabove defined.

The imidazoisindolones may be prepared by refluxing the reactants in a water-immiscible organic solvent such as toluene, benzene, xylene, chloroform, carbon tetrachloride or pyridine. The flask should be equipped with a water separator and the usual period of reflux is 12—24 hours. The solution is then extracted with water and the organic layer is evaporated *in vacuo* to a solid residue. On recrystallisation from a solvent such as ethanol, ethyl acetate, hexane-acetone or chloroform, the imidazoisindolone is obtained in good yield.

The final products made from the new intermediates of the invention contain salts with pharmaceutically acceptable acids and the invention also provides such salts. Suitable acids for the formation of acid addition salts include hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, lactic, citric, tartaric, maleic, gluconic, benzenesulphonic, toluenesulphonic, methanesulphonic and similar inorganic and organic acids.

The invention further provides a pharmaceutical composition which comprises a pharmaceutically active compound of formula VII or VIII, derived from the new compounds of formula I where R^4 and R^5 are hydrogen, which active compound may, for example, be micronised, and a pharmaceutically acceptable carrier.

Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a

solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99%, preferably 10—80%, by weight of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, a sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 1 mg. or less to 500 mg. or more, according to the particular need and the activity of the active ingredient. The invention also includes the unit dosage form of compounds of formulae VII and VIII, made from compounds of formula I, in the absence of a carrier.

The following examples have been added to illustrate the invention:

Example 1

A solution of 50 g. of *o*-(*p*-chlorobenzoyl)benzoic acid, 100 ml. of toluene and 40 ml. of 1,2-diamino-2-methyl-propane is refluxed in a flask equipped with a water separator. After refluxing for seventeen hours, the solution is extracted with water and the organic portion evaporated *in vacuo* to a solid residue. On recrystallisation from ethanol, there is obtained 9b-(*p*-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 132—40°C.

Anal. Calc'd for $C_{18}H_{17}ClN_2O$: C, 69.34; H, 5.17; N, 8.99; Cl, 11.11.

Found: C, 69.21; H, 5.40; N, 8.65; Cl, 11.30.

In a similar manner, reacting appropriate 1,1-dialkylethylene diamines with *o*-benzoylbenzoic acids, there are obtained:

1,2,3,9b - tetrahydro - 2,2 - diethyl - 9b - phenyl - 5H - imidazo[2,1-*a*]isoindol-5-one;

2,2 - diethyl - 9b - (3,4 - diiodophenyl) - 1,2,3,9b - tetrahydro - 5H - imidazo[2,1-*a*]isoindol-5-one;

9b - (3,4 - diethoxyphenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H - imidazo[2,1-*a*]isoindol-5-one;

7 - amino - 9b - (*p* - fluorophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dipropyl - 5H - imidazo[2,1-*a*]isoindol-5-one; and

7 - chloro - 9b - (4 - ethylphenyl) - 1,2,3,9b - tetrahydro - 2 - methyl - 2 - propyl-5H-imidazo[2,1-*a*]isoindol-5-one.

Example 2

A solution of 50 g. of *o*-(*p*-fluorobenzoyl)benzoic acid, 150 ml. of toluene and 75 ml. of 1,2-diamino-2-methyl-propane is refluxed in a flask equipped with a water

separator. After refluxing for nineteen hours the solution is extracted with water. The toluene layer is evaporated to dryness and the residue is recrystallised from aqueous alcohol to obtain 9b-(*p*-fluorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-*a*]isoindol-5-one, m.p. 108—110°C.

Anal. Calc'd for $C_{18}H_{17}N_2FO$: C, 72.95; H, 5.78; N, 9.45.

Found: C, 72.83; H, 5.86; N, 9.45.

Similarly, 1,2,3,9b-tetrahydro-2,2,7-trimethyl-9b-phenyl-5H-imidazo[2,1-*a*]isoindol-5-one and 1,2,3,9b-tetrahydro-2,2-dimethyl-9b-phenyl-9-propyl-5H-imidazo[2,1-*a*]isoindol-5-one are prepared.

Example 3

A solution of 40 g. of *o*-benzoylbenzoic acid, 60 ml. of 1,2-diamino-2-methylpropane, and 150 ml. of toluene is refluxed in a flask equipped with a water separator. After refluxing eight hours the solution is extracted with water and the toluene portion is evaporated to dryness. The residue is recrystallised from ethanol to obtain 1,2,3,9b-tetrahydro-9b-phenyl-2,2-dimethyl-5H-imidazo-[2,1-*a*]isoindol-5-one, m.p. 146—9°C.

Anal. Calc'd for $C_{18}H_{17}N_2O$: C, 77.67; H, 6.52; N, 10.07.

Found: C, 77.35; H, 6.88; N, 10.15.

Repeating the above procedure, the following compounds are prepared:

9b - (3,4 - dichlorophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H - imidazo-[2,1-*a*]isoindol-5-one;

2,2 - diethyl - 9b - (*p* - fluorophenyl) - 1,2,3,9b - tetrahydro - 5H - imidazo[2,1-*a*]isoindol-5-one; and

1,2,3,9b - tetrahydro - 2,2 - dimethyl - 9b - (*p* - tolyl) - 5H - imidazo[2,1-*a*]isoindol-5-one.

Example 4

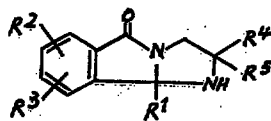
A solution of 35 g. of *o*-(*p*-bromobenzoyl)benzoic acid, 125 ml. of toluene, and 50 ml. of 1,2-diamino-2-methylpropane is refluxed in a flask equipped with a water separator. After refluxing six hours, the solution is extracted with water. The toluene is evaporated to dryness *in vacuo*. On recrystallisation from dilute alcohol there is obtained 9b - (*p* - bromophenyl) - 1,2,3,9b - tetrahydro - 2,2 - dimethyl - 5H - imidazo[2,1-*a*]isoindol-5-one, m.p. 133—5°C.

Anal. Calc'd for $C_{18}H_{15}N_2BrO$: C, 60.51; H, 4.80; N, 7.84.

Found: C, 60.80; H, 4.91; N, 7.91.

Example 5

When the procedure of Examples 1,4 is repeated to condense an appropriate 1,1-dialkylethylene diamine with an *o*-aroylbenzoic acid, the following 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-*a*]isoindol-5-ones are produced:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are as follows:

R ¹	R ²	R ³	R ⁴	R ⁵
<i>p</i> -iodophenyl	7-bromo	hydrogen	methyl	methyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl
2-thienyl	7-methoxy	8-methoxy	butyl	butyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl
2-pyridyl	7-fluoro	8-fluoro	methyl	butyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl
2-furyl	7-ethyl	hydrogen	methyl	methyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl
phenyl	8-ethyl	hydrogen	methyl	methyl
2,5-dibutylphenyl	hydrogen	hydrogen	methyl	methyl
phenyl	hydrogen	hydrogen	ethyl	methyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl

Example 6

A mixture of 30 g. of 9b-(p-chlorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example 1, and 100 ml. of 50% hydrochloric acid is heated in a steam bath. Dissolution occurs on heating for ten minutes and then a solid begins to precipitate immediately. The mixture is cooled, filtered and washed with acetone to obtain 2-(2-amino-2-methylpropyl)-3-(p-chlorophenyl)-3-hydroxyphthalimidine hydrochloride, m.p. 230—2°C.

This hydrochloride salt is neutralised with sodium carbonate solution to obtain the corresponding phthalimidine base, m.p. 208—10°C., (recrystallised from ethanol).
Anal. Calc'd for $C_{18}H_{19}N_2ClO_2$: C, 65.35; H, 5.79; N, 8.47; Cl, 10.72.
Found: C, 65.48; H, 5.75; N, 8.43; Cl, 10.88.

Similarly, the following compounds are prepared from the other 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-ones of Example I:

- 2-(2-amino-2-ethylbutyl)-3-hydroxy-3-(3,4-diiodophenyl)phthalimidine;
- 2-(2-amino-2-methylpropyl)-3-(3,4-diethoxyphenyl)-3-hydroxyphthalimidine;
- 2-(2-amino-2-methylbutyl)-3-(4-hexylphenyl)-3-hydroxyphthalimidine;
- 6-amino-2-(2-amino-2-propylpentyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine;
- and
- 2-(2-amino-2-methylpentyl)-6-chloro-3-(p-ethylphenyl)-3-hydroxyphthalimidine.

Example 7

A mixture of 45 g. of 9b-(p-fluorophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example 2, and 150 ml. of 50% hydrochloric acid is heated in a steam bath. After ten minutes a clear solution forms; then solid begins to precipitate. The mixture is heated for an additional ten minutes, then cooled, filtered and washed with acetone. The solid obtained is 2-(2-amino-2-methylpropyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine hydrochloride, hydrate, m.p. 177—180°C. dec.

The hydrochloride salt is neutralised with sodium carbonate solution to obtain the phthalimidine base, m.p. 196—9°C.

Anal. Calc'd for $C_{18}H_{19}N_2FO_2$: C, 68.78; H, 6.09; N, 8.91.
Found: C, 68.83; H, 6.18; N, 8.99.

Similarly, 2-(2-amino-2-methylpropyl)-3-hydroxy-6-methyl-3-phenylphthalimidine and 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenyl-4-propylphthalimidine are prepared.

Example 8

A mixture of 47 g. of 1,2,3,9b-tetrahydro-9b-phenyl-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one, as prepared in Example 3, and 150 ml. of 50% hydrochloric acid is heated on a steam bath. A clear solution forms within fifteen minutes and then reprecipitation occurs. After heating an additional five minutes, the mixture is cooled and filtered to obtain 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenylphthalimidine hydrochloride, m.p. 252—5°C. (dec.).

The above-prepared hydrochloride salt is neutralised with sodium carbonate solution to obtain the phthalimidine base, m.p. 172—3°C.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.94; H, 6.80; N, 9.45.
Found: C, 72.80; H, 6.93; N, 9.32.

Repeating the above procedure, the following compounds are prepared:

- 2-(2-amino-2-methylpropyl)-3-(3,4-dichlorophenyl)-3-hydroxyphthalimidine;
- 2-(2-amino-2-ethylbutyl)-3-(p-fluorophenyl)-3-hydroxyphthalimidine; and
- 2-(2-amino-2-methylpropyl)-3-hydroxy-3-(p-tolyl)-phthalimidine.

Example 9

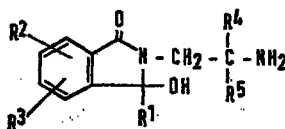
A mixture of 33 g. of 9b-(p-bromophenyl)-1,2,3,9b-tetrahydro-2,2-dimethyl-5H-imidazo[2,1-a]isoindol-5-one and 120 ml. of 50% hydrochloric acid is heated in a steam bath. A clear solution forms within ten minutes and then reprecipitation occurs. After heating an additional ten minutes, the mixture is cooled and filtered to obtain 2-(2-amino-2-methylpropyl)-3-(p-bromophenyl)-3-hydroxyphthalimidine hydrochloride, m.p. 227—230°C. (dec.).

The above-prepared hydrochloride salt is neutralised with sodium carbonate solution to obtain the phthalimidine base, m.p. 194—6°C.

Anal. Calc'd for $C_{18}H_{19}N_2BrO_2$: C, 57.61; H, 5.10; N, 7.46.
Found: C, 57.37; H, 5.19; N, 7.29.

Example 10

When the procedure of Examples 6—9 is repeated to hydrolyse an appropriate 2,2-dialkyl-9b-aryl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one, as described in Example 5, the corresponding 2-(2-amino-2,2-dialkylethyl)-3-aryl-3-hydroxyphthalimidine hydrohalide is afforded which is then neutralised to produce the base thereof having the formula:



wherein R¹, R², R³, R⁴ and R⁵ are as follows:

R ¹	R ²	R ³	R ⁴	R ⁵
<i>p</i> -iodophenyl	7-bromo	hydrogen	methyl	methyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl
2-thienyl	7-methoxy	8-methoxy	butyl	butyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl
2-pyridyl	7-fluoro	8-fluoro	methyl	butyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl
2-furyl	7-ethyl	hydrogen	methyl	methyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl
phenyl	8-ethyl	hydrogen	methyl	methyl
2,5-dibutylphenyl	hydrogen	hydrogen	methyl	methyl
phenyl	hydrogen	hydrogen	ethyl	methyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl

Example 11

The acid chloride prepared from 26 g. of *o*-(*p*-chlorobenzoyl)benzoic acid is dissolved in 40 ml. of acetone and is added dropwise with stirring to 35 ml. of 1,2-diamino-2-methylpropane and 150 ml. of pyridine. The mixture is stirred and refluxed for one hour and then evaporated to dryness *in vacuo*. The residue is slurried with water and separated by filtration. On recrystallisation from ethanol there is obtained 2-(2-amino-2-methylpropyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine, m.p. 208—210°C.

In a similar manner, the acid halides of the appropriate *o*-benzoylbenzoic acids are acylated to afford the following compounds:

2-(2-amino-2-methylpropyl)-3-(*p*-fluorophenyl)-3-hydroxyphthalimidine, m.p. 177—180°C.;

2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenylphthalimidine, m.p. 172—3°C.;

and

2-(2-amino-2-methylpropyl)-3-(*p*-bromophenyl)-3-hydroxyphthalimidine, m.p. 194—6°C.

Example 12

A mixture of 35 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine hydrochloride, as prepared in Example 6, 25 g. of *p*-toluenesulphonyl chloride and 125 ml. of anhydrous pyridine is refluxed for three hours. The solution is evaporated to dryness and the residue partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to a solid residue. On recrystallisation from ethanol there is obtained *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide, m.p. 225—7°C.

Anal. Calc'd for $C_{25}H_{23}ClN_2O_4S$: C, 61.91; H, 5.20; N, 5.78; Cl, 7.31; S, 6.61. Found: C, 61.83; H, 5.00; N, 5.63; Cl, 7.43; S, 6.82.

A solution of 15 g. of the above-prepared *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide and 40 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The reaction mixture which contains the sulphate salt of 4'-chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several volumes of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation there is obtained 5-(*p*-chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 199—202°C.

A suspension of 1.5 g. of the above-prepared 5-(*p*-chlorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol in 25 ml. of absolute ethanol is saturated with hydrogen chloride. The solution is evaporated to dryness *in vacuo*. The residue is triturated with ethyl acetate and separated by filtration. On recrystallisation from an ethanol-ethyl acetate mixture, there is obtained 4'-chloro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 235—8°C. dec.

Anal. Calc'd for $C_{18}H_{17}N_2OCl.HCl$: C, 61.90; H, 5.19; N, 8.20; Cl, 20.30. Found: C, 61.59; H, 5.29; N, 8.20; Cl, 20.53.

IR (KBr) 1670 cm^{-1} , 2558—2941 cm^{-1} .

U.V. (Isopropanol) max. 263 $m\mu$ ($\epsilon = 12,460$).

Example 13

A mixture of 32 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-fluorophenyl)-3-hydroxyphthalimidine, 22 g. of *p*-toluenesulphonyl chloride and 200 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness *in vacuo* and the residue is partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to dryness. The residue is recrystallised from ethanol to obtain *N*-(2-[3-(*p*-fluorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluene-sulphonamide, m.p. 206—9°C.

Anal. Calc'd for $C_{25}H_{23}N_2FOS$: C, 64.09; H, 5.37; N, 6.30.

Found: C, 64.25; H, 5.39; N, 6.30.

A solution of 22 g. of *N*-(2-[3-(*p*-fluorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide, and 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The mixture which contains the sulphate salt of 4'-fluoro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl) benzophenone is quenched with several volumes of ice water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation from ethyl acetate there is obtained 5-(*p*-fluorophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 194—6°C.

Anal. Calc'd for $C_{18}H_{17}N_2FO$: C, 72.96; H, 5.78; N, 9.45.

Found: C, 72.88; H, 5.91; N, 9.45

IR (KBr) 1658 cm^{-1} , 2273—2278 cm^{-1}

U.V. (95% of EtOH) max 260 $m\mu$ ($\epsilon = 5,760$)
 max 272 $m\mu$ ($\epsilon = 5,000$)
 (pHl) max 252 $m\mu$ ($\epsilon = 13,000$)

On treating 5-(*p*-fluorophenyl)-2,3-dihydro-2,2-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride, there is obtained 4'-fluoro-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 203—5°C.

Anal. Calc'd for $C_{18}H_{17}N_2FO \cdot HCl$: C, 64.96; H, 5.45; N, 8.42.

Found: C, 64.79; H, 5.47; N, 8.39.

IR (KBr) 1658 cm^{-1} , 2600—2941 cm^{-1}

U.V. (isopropanol) max 250 $m\mu$ ($\epsilon = 12,100$).

EXAMPLE 14.

A mixture of 27.5 g. of 2-(2-amino-2-methylpropyl)-3-hydroxy-3-phenyl-phthalimidine, 20 g. of *p*-toluenesulphonyl chloride and 200 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness. The residue is triturated with water and separated by filtration. On recrystallisation from 95% ethanol there is obtained *N*-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide, m.p. 197—200°C.

Anal. Calc'd for $C_{25}H_{26}N_2SO_4$: C, 66.64; H, 5.81; N, 6.22.

Found: C, 66.30; H, 5.70; N, 6.13.

A solution of 17 g. of *N*-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide and 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The solution which contains the sulphate salt of 2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several volumes of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation from ethanol there is obtained 5-phenyl-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 211—212°C.

Anal. Calc'd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07.

Found: C, 77.44; H, 6.64; N, 9.87.

IR (KBr) 1645 cm^{-1} , 2273—2790 cm^{-1}

U.V. (95% EtOH) max 260 $m\mu$ ($\epsilon = 4,900$)
 max 272 $m\mu$ ($\epsilon = 4,440$)
 max 250 $m\mu$ ($\epsilon = 13,480$)

On treating 5-phenyl-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride, there is obtained 2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)-benzophenone, hydrochloride, m.p. 174—6°C.

Anal. Calc'd for $C_{18}H_{18}N_2O \cdot HCl$: C, 68.68; H, 6.08; N, 8.90.

Found: C, 68.86; H, 6.07; N, 8.87.

IR (KBr) 1645 cm^{-1} , 2564—3077 cm^{-1}

U.V. (isopropanol) max. 249 $m\mu$ ($\epsilon = 12,940$)

EXAMPLE 15.

A mixture of 16.8 g. of 2-(2-amino-2-methylpropyl)-3-(*p*-bromophenyl)-3-hydroxyphthalimidine, 10 g. of *p*-toluene-sulphonyl chloride and 100 ml. of pyridine is refluxed for eight hours. The solution is evaporated to dryness and the residue is partitioned between ethyl acetate and water. The ethyl acetate portion is evaporated to a solid residue. On recrystallisation from ethanol there is obtained *N*-(2-[3-(*p*-bromophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide, m.p. 234—7°C.

Anal. Calc'd for $C_{25}H_{25}N_2BrSO_4$: C, 56.71; H, 4.76; N, 5.30.

Found: C, 56.91; H, 4.65; N, 5.45.

A solution of 11 g. of *N*-(2-[3-(*p*-bromophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide and 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The solution which contains the sulphate salt of 4'-bromo-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone is quenched with several volumes of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation from ethyl acetate, there is obtained 5-(*p*-bromophenyl)-2,3-dihydro-2,2(or 3,3)-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 192—4°C.

Anal. Calc'd for $C_{17}H_{17}N_2BrO$: C, 60.51; H, 4.79; N, 7.85.

Found: C, 60.51; H, 4.82; N, 7.82.

IR (KBr) 1639 cm^{-1} , 2273—2778 cm^{-1}

13

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13

U.V. (95% EtOH) max. 224 $m\mu$ ($\epsilon=24,400$)
 max. 263 $m\mu$ ($\epsilon=6,780$)
 max. 275 $m\mu$ ($\epsilon=6,400$)
 (pH1) max. 267 $m\mu$ ($\epsilon=13,640$)

5

On treating 5-(*p*-bromophenyl)-2,3-dihydro-2,2-dimethyl-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride there is obtained 4'-bromo-2-(4,4(5,5)-dimethyl-2-imidazolin-2-yl)benzophenone, hydrochloride, m.p. 222—5°C.

5

Anal. Calc'd for $C_{16}H_{17}BrN_2O.HCl$: C, 54.91; H, 4.61; N, 7.12.

Found: C, 55.09; H, 4.67; N, 6.75.

10

IR (KBr) 1661 cm^{-1} , 2500—2941 cm^{-1}

10

U.V. (Isopropanol) max. 267 $m\mu$ ($\epsilon=14,500$)

EXAMPLE 16.

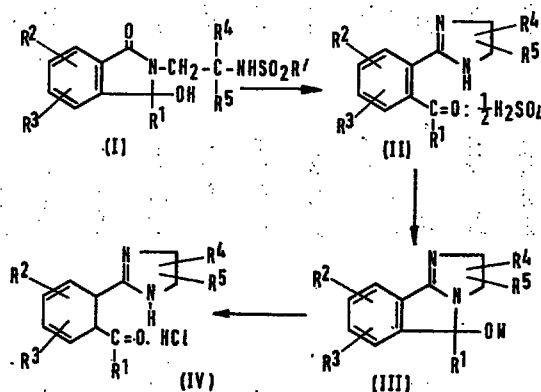
15

When the procedure of Examples 13—15 is repeated to react appropriate 2-(2-amino-2-alkylalkyl-3-aryl-3-hydroxyphthalimidine hydrohalides with aryl or alkyl sulphonyl halides, there are afforded the following *N*-([3-aryl-3-hydroxy-2-phthalimidinyl]-1,1-dialkylalkyl)sulphonamides (I) which are then contacted with sulphuric acid to afford appropriate sulphate salts of 4,4(5,5)-dialkyl-2-imidazolin-2-yl-phenyl aroyl compounds (II) which are neutralised to afford appropriate 2,2(or 3,3)-dialkyl-5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (III) which may be acidified, e.g. with hydrochloric acid, to afford the corresponding 4,4(5,5)-dialkyl-2-imidazolin-2-yl-phenyl ketone compound acid-addition salts (IV), e.g. hydrochlorides, which compounds (I), (II), (III) and (IV) are depicted by the following formulae:

15

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wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^7 are defined below:

R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶
<i>p</i> -iodophenyl	7-bromo	Hydrogen	methyl	methyl	ethyl
3,4-dimethylphenyl	8-methoxy	hydrogen	methyl	ethyl	phenyl
<i>p</i> -methoxyphenyl	7-chloro	8-chloro	methyl	methyl	<i>p</i> -chlorophenyl
<i>m</i> - and <i>p</i> -trifluoromethylphenyl	7-methylamino	hydrogen	ethyl	ethyl	phenyl
2,5-dibromophenyl	7-methyl	8-methyl	methyl	methyl	<i>p</i> -bromophenyl
3,4-dimethoxyphenyl	6-ethoxy	hydrogen	methyl	methyl	4-ethylphenyl
2-thienyl	7-methoxy	8-methoxy	butyl	butyl	3,4-dimethylphenyl
<i>p</i> -propoxyphenyl	9-iodo	hydrogen	methyl	methyl	phenyl
2-pyridyl	7-fluoro	8-fluoro	methyl	butyl	2,5-dichlorophenyl
2,5-dipropoxyphenyl	hydrogen	hydrogen	methyl	methyl	<i>n</i> -pentyl
2-furyl	7-ethyl	hydrogen	methyl	methyl	3,4-dibromophenyl
3,4-diethylphenyl	8-propylamino	hydrogen	methyl	methyl	<i>p</i> -iodophenyl
5,6,7,8-tetrahydro-2-naphthyl	7-ethyl	9-ethyl	propyl	ethyl	<i>p</i> -methoxyphenyl
<i>o</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -iodiphenyl
phenyl	8-ethyl	hydrogen	methyl	methyl	3,4-difluorophenyl
2,5-dibutylphenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl
phenyl	hydrogen	hydrogen	ethyl	methyl	3,4-diethylphenyl
<i>p</i> -chlorophenyl	7-ethoxy	hydrogen	methyl	methyl	<i>p</i> -fluorophenyl
<i>m</i> -chlorophenyl	hydrogen	hydrogen	methyl	methyl	<i>p</i> -ethoxyphenyl

EXAMPLE 17.

A solution of 21.5 g. of 2-(2-aminoethyl)-3-(*p*-chlorophenyl)-3-hydroxyphthalimidine, 13.3 g. of *p*-toluenesulphonyl chloride and 150 ml. of pyridine is allowed to stand at room temperature for eighteen hours. The mixture is quenched with water and extracted with ethyl acetate. The ethyl acetate portion is evaporated to dryness and the residue crystallizes on standing for three days. On recrystallisation from aqueous ethanol there is obtained *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide, m.p. 133—6°C.

Anal. Calc'd for $C_{22}H_{21}N_2O_4S$: C, 60.32; H, 4.84; N, 6.12; Cl, 7.74.

Found: C, 60.54; H, 4.50; N, 6.08; Cl, 7.56.

A solution of 18 g. of *N*-(2-[3-(*p*-chlorophenyl)-3-hydroxy-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide and 50 ml. of 90% sulphuric acid is allowed to stand at room temperature for forty-five minutes. The solution containing the sulphate salt of 4'-chloro-2-(2-imidazolin-2-yl)-benzophenone is quenched with several volumes of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation from dimethylacetamide there is obtained 5-(*p*-chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 208—210°C. (dec.).

Anal. Calc'd for $C_{16}H_{12}N_2OCl$: C, 67.49; H, 4.60; N, 9.84; Cl, 12.45.

Found: C, 67.18; H, 4.32; N, 9.68; Cl, 12.70.

IR (KBr) 1645 cm^{-1} , 2380—3000 cm^{-1}

U.V. (95% EtOH) max. 223 $m\mu$ (ϵ = 19,000)

infl. 242.5 $m\mu$ (ϵ = 8,300)

max. 268.5 $m\mu$ (ϵ = 4,400)

max. 272 $m\mu$ (ϵ = 4,400)

pH1) max. 251 $m\mu$ (ϵ = 11,000)

max. 264 $m\mu$ (ϵ = 10,800)

On treating 5-(*p*-chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride, there is obtained 4'-chloro-2-(2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 170—2°C.

Anal. Calc'd for $C_{16}H_{13}N_2ClO \cdot HCl$: C, 59.80; H, 4.40; N, 8.72; Cl, 22.08.

Found: C, 59.63; H, 4.50; N, 8.72; Cl, 21.79.

IR (KBr) 1647 cm^{-1} , 2300—3200 cm^{-1}

U.V. (95% EtOH) max. 252 $m\mu$ (ϵ = 12,100)

max. 265 $m\mu$ (ϵ = 12,300)

(Isopropanol) max. 264 $m\mu$ (ϵ = 11,000)

EXAMPLE 18.

When the procedure of Example 17 is repeated to react 2-(2-aminoethyl)-3-aryl-3-hydroxyphthalimidines or their hydrohalides with appropriate aryl or alkyl sulphonyl halides, there are afforded *N*-(2-[3-aryl-3-hydroxy-2-phthalimidinyl]alkyl) sulphonamides which are contacted with sulphuric acid to afford sulphate salts of 2-imidazolin-2-yl-phenyl aroyl compounds which are neutralised to yield the following 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols which are acidified, e.g. with hydrochloric acid, to produce the corresponding hereinafter listed 2-imidazolin-2-yl-phenyl ketone compound acid-addition salts, e.g. hydrochlorides.

5-Aryl-2,3-Dihydro-5-Imidazo[2,1- <i>a</i>]Isoindol-5-Ols	2-Imidazolin-2-Yl Phenyl Aroyl Compound Hydrochlorides
2,3-dihydro-5-(3',4'- diiodophenyl)-5H-imidazo- [2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)- 3',4'-diiodobenzophenone hydrochloride
5-(3',4'-diethoxyphenyl)- 2,3-dihydro-5H-imidazo- [2,1- <i>a</i>]isoindol-5-ol	3',4'-diethoxy-2-(2- imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-5-(4'-tolyl)- 5H-imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-4'- methylbenzophenone hydro- chloride
2,3-dihydro-5-(2-thienyl)- 5H-imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)phenyl- 2-thienyl ketone hydro- chloride
2,3-dihydro-8-methyl-5-phenyl- 5H-imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-4- methylbenzophenone hydro- chloride
2,3-dihydro-5-phenyl-6-propyl- 5H-imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-6- propylbenzophenone hydro- chloride
5-(4'-bromophenyl)-2,3- dihydro-5H-imidazo[2,1- <i>a</i>]- isoindol-5-ol	4'-bromo-2-(2-imidazolin- 2-yl)-benzophenone hydro- chloride
5-(3',4'-dichlorophenyl)- 2,3-dihydro-5H-imidazo- [2,1- <i>a</i>]isoindol-5-ol	3',4'-dichloro-2-(2- imidazolin-2-yl)benzophenone hydrochloride
5-(4'-fluorophenyl)-2,3- dihydro-5H-imidazo[2,1- <i>a</i>] isoindol-5-ol	4'-fluoro-2-(2-imidazolin- 2-yl)benzophenone hydro- chloride
7-bromo-2,3-dihydro-5-(4-tolyl)- 5H-imidazo[2,1- <i>a</i>]isoindol-5-ol	5-bromo-2-(2-imidazolin- 2-yl)-4'-methylbenzophenone hydrochloride
7,8-dibromo-5-(4-bromophenyl)- 2,3-dihydro-5H-imidazo[2,1- <i>a</i>] isoindol-5-ol	4,4',5-tribromo-2-(2- imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-5-(2,4-dimethoxy- phenyl)-5H-imidazo[2,1- <i>a</i>]- isoindol-5-ol	2-(2-imidazolin-2-yl)-2',4'- dimethoxybenzophenone hydrochloride
5-(2,4-dibromophenyl)-2,3- dihydro-5H-imidazo[2,1- <i>a</i>]- isoindol-5-ol	2',4'-dibromo-2-(2-imidazo- lin-2-yl)benzophenone hydrochloride

5-Aryl-2,3-Dihydro-5-Imidazo[2,1- <i>a</i>]Isoindol-5-Ols	2-Imidazolin-2-yl Phenyl Aryl Compound Hydrochlorides
2,3-dihydro-5-(5,6,7,8-tetrahydro-2-naphthyl)-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)phenyl-(5,6,7,8-tetrahydro-2-naphthyl)ketone hydrochloride
5-(4-trifluoromethylphenyl)-2,3-dihydro-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	4'-trifluoromethyl-2-(2-imidazolin-2-yl)benzophenone hydrochloride
5-(2-trifluoromethylphenyl)-2,3-dihydro-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2'-trifluoromethyl-2-(2-imidazolin-2-yl)benzophenone hydrochloride
5-furyl-2,3-dihydro-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	furyl-2-(2-imidazolin-2-yl)phenyl ketone hydrochloride
7-chloro-2,3-dihydro-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	5-chloro-2-(2-imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-8-methyl-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-4-methylbenzophenone hydrochloride
7-ethylamino-2,3-dihydro-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	5-ethylamino-2-(2-imidazolin-2-yl)benzophenone dihydrochloride
7,8-dichloro-2,3-dihydro-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	4,5-dichloro-2-(2-imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-7,8-dimethoxy-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-4,5-dimethoxybenzophenone hydrochloride
2,3-dihydro-5-(3-iodophenyl)-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-3'-iodobenzophenone hydrochloride
8- <i>n</i> -amyl-2,3-dihydro-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	4- <i>n</i> -amyl-2-(2-imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-5-phenyl-7-propyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-5-propylbenzophenone hydrochloride
8- <i>n</i> -butoxy-2,3-dihydro-5-phenyl-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	4- <i>n</i> -butoxy-2-(2-imidazolin-2-yl)benzophenone hydrochloride
2,3-dihydro-5-(3,4-dimethylphenyl)-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-3',4'-dimethylbenzophenone hydrochloride
2,3-dihydro-5-(4-propoxyphenyl)-5 <i>H</i> -imidazo[2,1- <i>a</i>]isoindol-5-ol	2-(2-imidazolin-2-yl)-4'-propoxybenzophenone hydrochloride

EXAMPLE 19.

A solution of 10 g. of 2-(2-aminoethyl)-3-hydroxy-3-phenyl phthalimidine, 8 g. of *p*-toluenesulphonyl chloride and 50 ml. of pyridine is allowed to stand at room temperature for six hours. The mixture is quenched with water. The aqueous portion is separated and the oily residue is dissolved in ethyl acetate. The solution is extracted with water and then evaporated to dryness *in vacuo*. The residue solidifies on standing. On recrystallisation from ethanol there is obtained N-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide, m.p. 160—2°C.

Anal. Calc'd for $C_{23}H_{22}N_2O_5S$: C, 65.38; H, 5.24; N, 6.63; S, 7.59.

Found: C, 65.22; H, 4.98; N, 6.52; S, 7.48.

EXAMPLE 20.

A solution of 7 g. of N-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide and 20 ml. of 90% sulphuric acid is allowed to stand at room temperature for 30 minutes. The solution is quenched with ice-water and extracted with ethyl acetate. The aqueous portion is neutralised with concentrated sodium hydroxide solution. The solid is separated and washed with water. On recrystallisation from dimethylacetamide there is obtained 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol, m.p. 207—210°C. (dec.).

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.63; N, 11.20.

Found: C, 76.63; H, 5.66; N, 11.00.

IR (KBr) 1645 cm^{-1} , $2300\text{--}3000\text{ cm}^{-1}$

U.V. (95% EtOH) inf. $225\text{ m}\mu$ ($\epsilon = 14,900$)

max. $268\text{ m}\mu$ ($\epsilon = 4,200$)

(pH1) max. $250\text{ m}\mu$ ($\epsilon = 13,500$)

On treating 5-phenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol with hydrogen chloride, there is obtained 2-(2-imidazolin-2-yl)benzophenone hydrochloride, m.p. 195—7°C. (dec.).

Anal. Calc'd for $C_{16}H_{14}N_2O.HCl$: C, 67.03; H, 5.27; N, 9.77; Cl, 12.36.

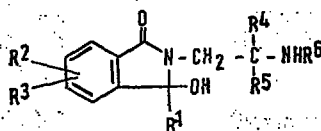
Found: C, 66.88; H, 5.33; N, 9.83; Cl, 12.50.

IR (KBr) 1650 cm^{-1} , $2400\text{--}3200\text{ cm}^{-1}$

U.V. (95% EtOH) max. $250\text{ m}\mu$ ($\epsilon = 12,800$).

WHAT WE CLAIM IS:—

1. A compound having the general formula:



wherein R^1 is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R^2 is hydrogen, halogen, amino, lower alkylamino, lower alkyl or lower alkoxy; R^3 is hydrogen when R^2 and R^4 are dissimilar and when R^2 and R^3 are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; R^4 and R^5 are hydrogen or (lower)alkyl and R^6 is (lower)alkylsulphonyl, phenylsulphonyl, monohalophenylsulphonyl, dihalophenylsulphonyl, mono(lower)alkylphenylsulphonyl, di(lower)alkylphenylsulphonyl or (lower)alkoxyphenylsulphonyl.

2. A compound according to Claim 1 in which R^4 and R^5 are methyl groups.

3. A compound according to Claim 1 in which R^4 and R^5 are both hydrogen.

4. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from phenyl, *m*-chlorophenyl, *p*-chlorophenyl and *p*-fluorophenyl.

5. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from *p*-iodophenyl, *p*-bromophenyl, *o*-chlorophenyl, 3,4-diiodophenyl, 3,4-dichlorophenyl, 2,5-dibromophenyl and *m*- and *p*-trifluoromethylphenyl.

6. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from *p*-tolyl, 3,4-dimethylphenyl, *p*-methoxyphenyl, 3,4-dimethoxyphenyl, 2-thienyl, 2-pyridyl and 2-furyl.

7. A compound according to any one of Claims 1 to 6, wherein R^2 and R^3 both represent hydrogen.

EXAMPLE 19.

A solution of 10 g. of 2-(2-aminoethyl)-3-hydroxy-3-phenyl phthalimidine, 8 g. of *p*-toluenesulphonyl chloride and 50 ml. of pyridine is allowed to stand at room temperature for six hours. The mixture is quenched with water. The aqueous portion is separated and the oily residue is dissolved in ethyl acetate. The solution is extracted with water and then evaporated to dryness *in vacuo*. The residue solidifies on standing. On recrystallisation from ethanol there is obtained N-(2-[3-phenyl-3-hydroxy-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide, m.p. 160—2°C.

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Anal. Calc'd for $C_{16}H_{11}N_3O$: C, 76.77; H, 5.63; N, 11.20.

Found: C, 76.63; H, 5.66; N, 11.00.

IR (KBr) 1645 cm^{-1} , $2300\text{--}3000\text{ cm}^{-1}$

U.V. (95% EtOH) inf. $225\text{ m}\mu$ ($\epsilon = 14,900$)

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(pH1) max. $250\text{ m}\mu$ ($\epsilon = 13,500$)

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Anal. Calc'd for $C_{16}H_{11}N_2O.HCl$: C, 67.03; H, 5.27; N, 9.77; Cl, 12.36.

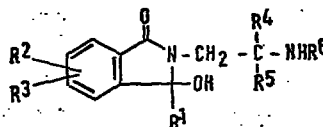
Found: C, 66.88; H, 5.33; N, 9.83; Cl, 12.50.

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U.V. (95% EtOH) max. $250\text{ m}\mu$ ($\epsilon = 12,800$).

WHAT WE CLAIM IS:—

1. A compound having the general formula:



wherein R^1 is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R^2 is hydrogen, halogen, amino, lower alkylamino, lower alkyl or lower alkoxy; R^3 is hydrogen when R^2 and R^3 are dissimilar and when R^2 and R^3 are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; R^4 and R^5 are hydrogen or (lower)alkyl and R^6 is (lower)alkylsulphonyl, phenylsulphonyl, monohalophenylsulphonyl, dihalophenylsulphonyl, mono(lower)alkylphenylsulphonyl, di(lower)alkylphenylsulphonyl or (lower)alkoxyphenylsulphonyl.

2. A compound according to Claim 1 in which R^4 and R^5 are methyl groups.

3. A compound according to Claim 1 in which R^4 and R^5 are both hydrogen.

4. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from phenyl, *m*-chlorophenyl, *p*-chlorophenyl and *p*-fluorophenyl.

5. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from *p*-iodophenyl; *p*-bromophenyl; *o*-chlorophenyl; 3,4-diiodophenyl; 3,4-dichlorophenyl; 2,5-dibromophenyl and *m*- and *p*-trifluoromethylphenyl.

6. A compound according to any one of Claims 1 to 3, wherein R^1 is selected from *p*-tolyl; 3,4-dimethylphenyl; *p*-methoxyphenyl; 3,4-dimethoxyphenyl; 2-thienyl; 2-pyridyl and 2-furyl.

7. A compound according to any one of Claims 1 to 6, wherein R^2 and R^3 both represent hydrogen.



8. A compound according to any one of Claims 1 to 6, wherein R² is selected from fluorine, bromine, chlorine, iodine, methoxy, ethoxy, methyl and ethyl.

9. A compound according to any one of Claims 1 to 8, wherein R⁶ is *p*-tolylsulphonyl.

10. A compound according to any one of Claims 1 to 8, wherein R⁶ is selected from ethylsulphonyl; *n*-pentylsulphonyl; phenylsulphonyl; *p*-fluorophenylsulphonyl; *p*-chlorophenylsulphonyl; *p*-bromophenylsulphonyl; *p*-iodophenylsulphonyl; 2,5-dichlorophenylsulphonyl; 3,4-dibromophenylsulphonyl and 3,4-difluorophenylsulphonyl.

11. A compound according to any one of Claims 1 to 8, wherein R⁶ is selected from 4-ethylphenylsulphonyl; 3,4-dimethylphenylsulphonyl; 3,4-diethylphenylsulphonyl; *p*-methoxyphenylsulphonyl; and *p*-ethoxyphenylsulphonyl.

12. *N*-(2-[3-(*p*-Chlorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide.

13. *N*-(2-[3-(*p*-Fluorophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide.

14. *N*-(2-[3-Hydroxy-3-phenyl-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide.

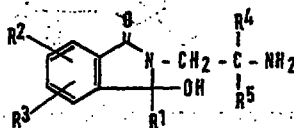
15. *N*-(2-[3-(*p*-Bromophenyl)-3-hydroxy-2-phthalimidinyl]-1,1-dimethylethyl)-*p*-toluenesulphonamide.

16. *N*-(2-[3-(*p*-Chlorophenyl)-3-hydroxy-2-phthalimidinyl]-ethyl)-*p*-toluenesulphonamide.

17. *N*-(2-[3-Hydroxy-3-phenyl-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide.

18. A compound according to Claim 1 substantially as described herein and shown with reference to the Examples.

19. A process for the preparation of a compound as claimed in Claim 1, which comprises reacting a compound having the formula



wherein R¹, R², R³, R⁴ and R⁵ are as defined in Claim 1, with a sulphonyl halide of the formula:



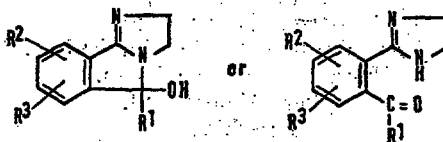
wherein R⁶ is as defined in Claim 1 and X is halogen.

20. A process according to Claim 19, where X is chlorine.

21. A process according to Claim 19, carried out substantially as described herein with reference to the Examples.

22. A compound as claimed in Claim 1 whenever prepared by a process according to any one of Claims 19 to 21.

23. A process for the preparation of a compound of formula



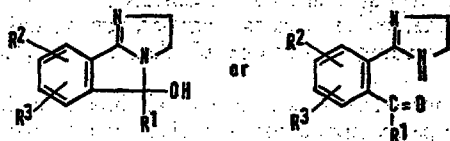
where desired in the form of an acid addition salt, wherein R¹, R² and R³ are as defined in Claim 1, wherein a compound according to Claim 3 is treated with a strong acid, and, if desired, an acid addition salt form of the product is converted into the free base form or a free base form into an acid addition salt form.

24. A process according to Claim 23, wherein the strong acid employed is sulphuric acid.

25. A process according to Claim 24 carried out substantially as described herein with reference to the examples.

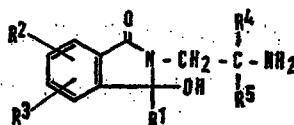
26. A compound of formula



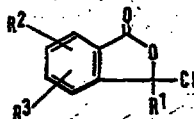


where desired in the form of an acid addition salt, wherein R^1 , R^2 and R^3 are as defined in claim 1, whenever prepared according to a process as claimed in any one of Claims 23 to 25.

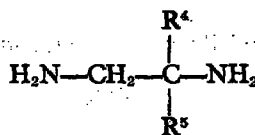
27. A process for the preparation of a compound having the general formula



wherein R^1 , R^2 and R^3 are as defined in Claim 1 and R^4 and R^5 are (lower)alkyl, which comprises contacting a compound of the formula:



wherein R^1 , R^2 and R^3 are as defined in Claim 1, with a compound of the formula:



wherein R^4 and R^5 are as defined above, in a solvent and refluxing the reaction mixture until the reaction is complete.

28. A process according to Claim 27 substantially as described herein and shown with reference to the Examples.

29. A compound prepared by a process according to Claim 27 or 28.

30. A pharmaceutical composition comprising a compound according to Claim 26 in association with a pharmaceutically acceptable carrier.

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